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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/989,725	11/20/2001	Avi J. Ashkenazi	P2730P1C71	2364

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HELLER EHRMAN WHITE & MCAULIFFE LLP
275 MIDDLEFIELD ROAD
MENLO PARK, CO 94025-3506

EXAMINER	
HAMUD, FOZIA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/989,725	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Fozia M Hamud	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *119-127,129-132 and 134-138* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *119-127,129-132 and 134-138* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *08/05/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicants' arguments and amendment, filed on 05 August 2004, is acknowledged.

1b. Receipt of Applicants' declaration under 37 C.F.R §1.132, filed by Dr. Sherman Fong filed on 05 August 2004, is also acknowledged.

Status of Claims:

1b. Claims 1-118 have been previously cancelled. Claims 128 and 133 are currently cancelled. Therefore, claims 119-127, 129-132 and 134-138 are pending and under consideration.

Information Disclosure Statement:

2a. Applicants are thanked for providing the references cited on the on the PTO-1449 form submitted by Applicants on 31 May 2002.

2. The following previous objection is withdrawn in light of Applicants amendments filed on 08/05/04:

2a. The rejection of claim 132 made under 35 U.S.C. 112, second paragraph, for not reciting specific hybridization conditions, is withdrawn, because the claim now recites said conditions.

2b. Applicants are thanked for deleting the "embedded hyperlink and/or other form of browser-executable code" from the specification.

Response to Applicants' arguments:

Applicant's arguments and amendment filed on 08/05/04 have been fully considered but were deemed persuasive in part. The remaining issues follow.

3. **Priority:**

3a. Applicants submit that the mixed lymphocyte reaction (MLR) assay was first disclosed in US Provisional Application 60/144758 filed on 20 July 1999, priority for which has been claimed in the current application. Applicants further submit that the subject matter defined in this application provides a specific and substantial utility or well established utility for the claimed invention, therefore, Applicants request that the current application be given the priority date of 20 July 1999.

This argument is not found persuasive. It is not disputed that US Provisional Application 60/144758 filed on 20 July 1999 discloses the MLR assay. However, the MLR assay fails to provide a specific and substantial utility or well established utility for the claimed invention to satisfy the requirements under 35 U.S.C. § 101/112, first paragraph, because it does not teach how one of ordinary skill in the art could use the claimed invention for the reasons discussed on paragraph 4 of the office action. Accordingly, the subject matter defined in claims 119-127, 129-132 and 134-138 is afforded an effective filing date of 11/15/2001, which is the filing date of the current application.

Claim Rejections - 35 U.S.C. § 101/112:

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4a. Claims 119-127, 129-132 and 134-138 stand rejected under 35 U.S.C. 101, for reasons of record, set forth in the office action mailed on 05/07/04, pages 3-8 and reiterated here, because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Applicants submit the following arguments regarding this rejection.

Applicants review the evidentiary standard regarding the legal presumption of utility. Applicants argue that the USPTO has not met its burden of overcoming the presumption of the truth of an asserted utility. This has been fully considered but is not found to be persuasive.

The examiner takes no issue with Applicant's discussion of the evidentiary standard regarding the legal presumption of utility. Furthermore, the rejection does not question the presumption of truth, or credibility, of the asserted utility.

Applicants argue that the legal standard with respect to in vitro or animal model data providing pharmacological activity has been commented on in Cross v. Iizuka, which states that an in vitro testing may establish a practical utility for the compound in question. Applicants also quote the MPEP 2107.03 (III) which relates that if reasonably correlated to the particular therapeutic or pharmaceutical utility, data generated using in vitro assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility compound, composition or process. Applicants also argue that immunostimulants are desirable in the treatment of cancer and in enhancing the effectiveness of previously identified

treatments for cancer. Applicants contend that the protein of the instant invention (PRO1375) could be used in the treatment of viral infections like HIV or Epstein Barr viral infections, and cancers like , melanoma.

These arguments have been considered fully but are not deemed persuasive. The fact situation in Cross et al. v. Iizuka et al. is different from the fact pattern of the instant case. In Cross v. Iizuka et al applications disclose imidazole derivative compounds which inhibit the synthesis of thromoxane synthetase, an enzyme that is involved in platelet aggregation. Platelet aggregation is associated with several deleterious conditions in mammalia, such as platelet thrombosis, pulmonary vasconstriction or vasospasm, inflammation, hypertension and collagen-induced thrombosis. However, in the instant case while the MLR is an in-vitro model for allogenic reaction, this assay has not been correlated with a specific disease or disorder. With respect to Applicants' argument that the protein of the instant invention could be used for treatment of melanoma, HIV or Epstein Barr viral infection, instant specification has not established a correlation between the claimed nucleic acid or the encoded protein and any of the above mentioned disorders. The specification has not shown that the protein of the instant invention has been used to treat any of these diseases. Furthermore, the state of the art is such that clearly no *in-vitro* immune assay predicts or correlates with in-vivo immunosuppressive efficacy. For example, Kahan states that there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from in-vitro systems to in-vivo conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column

2). Also, Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in-vitro does not result in a measurable response in-vivo (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) also demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation in-vitro nor produce immunosuppressive effects in-vivo, (see abstract and page 20). Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses in-vivo.

Additionally, difficulties arise in quantification when using MLR as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLR is typically used for determining histocompatibilty in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders.

Therefore, the MLR assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. There are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous

controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states that "decreases below control is considered to e a positive result for an inhibitory compound", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLR assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, as the above cited references disclose, thus, one of ordinary skill in the art would not expect an inhibitory effect in the MLR assay to correlate to a general suppressive effect on the immune system.

4b. Claims 119-127, 129-132 and 134-138 also stand rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a substantially asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. No biological activity was assayed or determined for the PRO1375 polypeptide. Although the specification describes the structure of PRO1375 polypeptide, and one of ordinary skill in the art can make antibodies against it, the skilled artisan would not know how to use said PRO1375 polypeptide or antibodies against it, because Applicants do not provide any information regarding biological activity or physiological characterization of

said polypeptide. The results of the MLR assay does not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not expect a stimulatory effect in the MLR assay to correlate to a general inhibitory effect on the immune system, absent evidence to the contrary.

Applicants argue that the pending claims are drawn to a genus of nucleic acids defined both by sequence and functional identity. This argument is not found persuasive, because although the claims recite both percent identity and functional language, the specification does not disclose a variant of the polypeptide of SEQ ID NO:418 that induces proliferation of stimulated T lymphocytes in a mixed lymphocyte reaction. Due to the large quantity of experimentation necessary to determine all the nucleic acids comprising a nucleotide sequence that is at least 80%, 85%, 90%, 95% or 99% identical to the nucleic acid of SEQ ID NO:417 and to screen for the ones that encode the polypeptide of SEQ ID NO:418, the lack of direction/guidance presented in the specification regarding which variants of the nucleic acid of SEQ ID NO:417 would retain the desired activity, the complex nature of the invention, the absence of working examples directed to variants of the nucleic acid of SEQ ID NO:417, the state of the prior art establishing that biological activity cannot be predicted based on structural similarity, the unpredictability of the effects of mutation on the structure and function of the claimed polypeptide, and the breadth of the claims which fail to recite particular biological activities, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 U.S.C. §102:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5a. Claims 119-127, 129-132 and 134-138 stand rejected under U.S.C. § 102(b) as being anticipated by MILLENNIUM BIOTHERAPEUTICS INC, (MILL), (WO 00/18904 June/2000); GENENTECH INC. (GETH), (WO 99/63088, September/1999); INCYTE (INCY), (WO 00/00610, June/2000); SAGAMI CHEM RES CENT (SAGA), (WO 00/00506, June/2000). Claims 119-125, 127 and 129-138 stand rejected under 35 U.S.C § 102(a) as being anticipated by HELIX RES IST. (HELI), (EP 1130094, September/2001).

Applicants reques that the instant application be afforded the priority date of 20 July 1999, (the filing date of the parent US Provisional Application 60/144758), which is prior to the publication dates of cited references, since both the current application and its priority application satisfy the requirements under 35 U.S.C. 112, first paragraph.

This argument is not found persuasive, because the instant invention is not entitled to the effective filing date of the priority application US Provisional Application 60/144758, filed on 20 July 1999, but is rather entitled to the filing date of the instant application, which is 11/15/2001, because neither the parent application not the current

application teach how to use the claimed invention in a manner that satisfies the requirements, under 35 U.S.C. 112, first paragraph. See paragraph 4 of this office action.

37 CFR 1.132 Declarations:

6a. Applicants present a declaration by Dr. Sherman Fong filed with the response under 37 CFR 1.132. In the declaration, Dr. Fong states that the MLR assay is designed to study a particularly important induction mechanism whereby responsive T-cells are cultured together with other lymphocytes that are allogenic. Dr. Fong submits that the MLR protocol of the present application, a suspension of PBMCs that includes responder T cells is cultured wit allogenic PBMCs that predominantly contain dendritic cells. Dr. Fong states that the stimulator PBMCs are irradiated at a dose of 3000 rads, and under these conditions only dendtritc cells are essentially the only remaining cells. Dr. Fong states that the dendritic cells are the most potent antigen presenting cells and they provide T cells with potent and needed accessory or co-stimulatory substances. Dr. Fong further states that once activated by dendritic cells, T cells are capable of interacting with other antigen presenting B cells and macrophages to produce additional immune responses from these cells. Dr. Fong also argues that the MLR assay of the present application is designed to measure the ability of a test substance to "drive" the dentritic cells to induce the proliferation of T-cells that are activated to co-stimulated in the MLR , and thus identifies immune stimulators that can boost the immune system to respond to a particular antigen that may not have been immunoloigcally active previously. Dr. Fong contends that such immune stimulators find clinical applications,

for example, IL-12 is a known immune stimulator, which was first identified in an MLR assay. However, in a recent cancer vaccine trial, researchers demonstrate that IL-12 treatment provided a superior results in comparison to using patients' own dentritic cells, treated with antigens, then cultured in vitro and returned to the patient to simulate anti-cancer response. Dr. Fong concludes that a polypeptide that inhibits T cell proliferation in the MLR assay where the activity is observed as 80% or less of the control, would be expected to find practical utility when an inhibition of the immune response is desired, such as in autoimmune diseases.

Dr. Fong's declaration is fully considered, but is not effective to overcome the rejection of claims 119-127, 129-132 and 134-138 made under 35 U.S.C. 101/112, first paragraph. It is not disputed that denrtiric cells are very potent antigen presenting cells and that they are able to prime naïve T-cells. However, the MLR assay in itself is not predictive of an in-vivo immune response, as was shown by Piccotti et al. (Transplantation 67: 1453-1460, 1999). Piccotti et al demonstrate that IL-12 markedly enhances alloantigen-specific immune function as determined by MLC, but this result in-vitro does not result in a measurable response in-vivo (i.e. failure to accelerate allograft rejection) (see abstract and page 1459). It is also correct that IL-12 is known to be an important immune stimulator with clinical applications and that it was first identified in an MLR assay. However, there are discrepancies of the effect of IL-12 on MLR assay depending on what stimulator is used. For example, Nishioka et al (Journal of leukocyte Biology, vol.73, pages 621-629, 2003), show that IL-12 effects differentially in human or mice cellular immunity in MLR stimulated by dentritic cells. Although, IL-12 is shown to

suppress MLR in mice, IL-12 stimulates MLR in humans. The researchers, demonstrate that murine dentritic cells produce nitric oxide (NO) while human dentritic cells did not, and that the production of NO by murine cells is responsible for the suppression of cellular responses, (see page 627, column 1). Therefore, the effect of IL-12 in the MLR assay alone was not sufficient to elucidate the role of this cytokine in the immune system. It was shown that IL-12 activates natural killer cells, stimulates T cells (as demonstrated by MLR assay), induces the production of interferon gamma and suppresses the growth of various tumors, (see Nishioka et al). Accordingly, the fact that an agent stimulates or inhibits T-cells in the MLR assay, is not sufficient to explain the role of said agent in the immune system. There is little doubt that, after further characterization the claimed antibody would have a specific, substantial and credible utility, however, further characterization is part of the invention and until it had been undertaken, the claimed invention is not supported by a specific asserted utility or a well established utility. The specification does not provide this further characterization, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the polypeptides of the instant invention is not in currently available form, the asserted utility is not substantial. For all of these reasons, the rejection claims 119-127, 129-132 and 134-138 made under 35 U.S.C. §101 and §112 is maintained.

Conclusion:

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia M Hamud whose telephone number is (571) 272-0884. The examiner can normally be reached on Monday, Thursday-Friday, 6:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Fozia Hamud
Patent Examiner
Art Unit 1647
8 November 2004

JANET ANDRES
PRIMARY EXAMINER